REMARKS

Entry of this amendment and favorable reconsideration of this application are respectfully requested.

Claims 1-23, 36, 44, 45, 85-92 and 96-99 are now pending in this application.

Claims 1-16, 19, 22-23, 36, 44-45, 85-90, and 96-99 have been rejected under 35 U.S.C. §112, first paragraph. This rejection is respectfully traversed.

In the previous Office Action, the basis for this rejection was stated as: "...the specification, while being enabling for an immunoglobulin molecule or fragment thereof wherein one or more CDRs are replaced with a TPO mimetic wherein the immunoglobulin molecule or fragment binds thrombopoietin receptor, does not reasonably provide enablement for an immunoglobulin molecule or fragment that comprises replacement of a CDR with a TPO mimetic and the molecule does not bind the thrombopoietin receptor."

The pending claims are directed to immunoglobulin molecules or fragments thereof. The specification includes detailed working examples of how to generate, select and test the activity of the claimed immunoglobulins. Beginning, e.g., on page 33 and continuing through page 36, Applicants' specification provides details regarding how to use antibodies prepared in accordance with the disclosure. Surely the level of detail provided in the specification would enable one skilled in the art to make and use the claimed immunoglobulins, whether a TPO mimetic, an EPO mimetic or any other biologically active peptide is used.

Nonetheless, Claim 1 has been amended to specifically recite embodiments wherein the immunoglobulin molecule or fragment thereof binds an EPO or TPO receptor. Claim 96 has been amended to specifically recite embodiments wherein the immunoglobulin molecule or fragment thereof binds a TPO receptor. These amendments are made in an attempt to advance and expedite prosecution. Applicants do not agree with the basis for the rejection under 35 U.S.C. §112, first paragraph for the reasons given herein and in the previous amendment. However, by limiting the claims to embodiments wherein the immunoglobulin molecule or fragment thereof binds an EPO or TPO receptor, it is respectfully submitted that the rejection of independent claims 1 and 96 (as well as all claims that depend therefrom, either directly or indirectly) becomes moot.

With respect to independent claims 44, 86 and 99, the recitation in each of these claims of a "biologically active peptide" does not implicate binding of any particular molecule, let alone an EPO or TPO receptor, specifically. Rather, patentability of these claims is premised upon the nature of the flanking groups, not upon a particular activity of the biologically active peptide. Accordingly, it is respectfully submitted that the stated basis of the rejection under 35 U.S.C. §112, first paragraph does not apply to independent claims 44, 86 and 99 (as well as all claims that depend therefrom, either directly or indirectly). Nonetheless, independent claims 44, 86 and 99 have been amended to recite that the immunoglobulin or fragment thereof exhibits a desirable biological activity. These amendments are made in an attempt to advance and expedite prosecution. Applicants do not agree with the basis for the rejection under 35 U.S.C. §112, first paragraph for the reasons given herein and in the previous amendment. It is respectfully submitted that this amendment to independent claims 44, 86 and 99 renders moot the rejection

thereof under 35 U.S.C. §112, first paragraph as well as the rejection of any claims which depend, either directly or indirectly from any of independent claims 44, 86 and 99.

Claims 1-16, 19, 22-23, 36, 44-45, 85-90 and 96-99 have been rejected under 35 U.S.C. §103 as being obvious over Barbas et al. WO 94/18221 ("the Barbas PCT") in view of Dower et al WO 96/40750 ("Dower") and a 1995 article by Barbas et al. ("the Barbas article") and an article by Helms et al. ("Helms"). This rejection is respectfully traversed.

In any obviousness rejection based on a combination of references, there must be some suggestion or motivation provided ***in the references*** to combine them in the manner described in the rejection to arrive at applicants' claimed invention. Here there is clearly no such suggestion or motivation in any of the references. If it is the examiner's position that there is some motivation or suggestion in the Barbas PCT (or any of the other applied reference) to insert a TPO or EPO mimetic into or in place of an antibody CDR, the examiner is respectfully requested to point out with particularity (by page/column and line) where in Barbas PCT such a teaching can be found. Applicants respectfully submit that no such motivation can be found in any of the applied references and that absent a suggestion in the references, the present rejection is improper and should be withdrawn. Applicants are the first to describe inserting a TPO or EPO mimetic into or in place of an antibody CDR, i.e., the subject matter to which claim 1 is directed.

While the Barbas PCT application contains a generic disclosure of incorporating a "binding site" into a CDR, Barbas's definition of "binding site" is "...any region of a protein or polypeptide that participates in protein-target molecule interactions..." (See Barbas PCT at page 16 lines 22-28) and embraces ***millions*** of polypeptides. This generic disclosure provides no motivation or suggestion whatsoever that it is desirable, practical or even possible to incorporate

the specifically recited EPO or TPO mimetics into an immunoglobulin molecule or fragment thereof. None of the specifically listed materials in Barbas provides one skilled in the art any motivation to incorporate a TPO or EPO mimetic into an immunoglobulin molecule or fragment thereof. In fact, at best, the Barbas PCT application may argruably make it obvious to try any one of the over a million polypeptides embraced by the definition of "binding site". However, it is hornbook patent law that "obvious to try" is not the appropriate standard for determining the obviousness of a claimed invention.

The Dower disclosure is limited to low molecular weight peptides and peptide mimetics, and nowhere teaches or suggests that it is desirable, practical or even possible to incorporate the specifically recited EPO or TPO mimetics into an immunoglobulin molecule or fragment thereof. (See the paragraph bridging pages 4 and 5 Dower.) Being specifically limited to "defined *low molecular weight* peptides and peptide mimetics", Dower lacks any teaching with respect to immunoglobulin molecules or fragments that bears on the obviousness of claim 1 and the claims that depend therefrom. Dower provides no motivation to incorporate the peptides and peptide mimetics disclosed therein into an immunoglobulin molecule or fragment thereof.

The Office Action argues that because Dower discloses "...the peptides can be constrained such as by adding cysteines to cyclize them for better affinity and binding...", it would be obvious to use the Dower peptides in the Barbas PCT methods. To the extent Applicants understand this statement, the argument set forth in the office action is believed to be logically flawed. To "cyclize" a peptide in no way suggests to one skilled in the art that the peptide should be inserted into an immunoglobulin molecule. For purposes of clarifying issues, applicants respectfully request that the examiner explain in greater detail how "adding cysteines

to cyclize" a peptide makes it obvious to put the peptide into or in place of a CDR region of an immunoglobulin molecules.

For the foregoing reasons and for those reasons stated in Applicants' previous amendment, the Barbas PCT application does not, alone or in combination with Dower, render obvious claim 1 or any of the claims depending therefrom. Accordingly, the rejection of claims 1-23, 36 and 90 under 35 U.S.C. §103 is deemed appropriate and is respectfully requested.

With respect to the presently pending claims that recite inserting a biologically active peptide having as its core sequence SEQ ID NO: 1 (i.e., claims 18-21, 91, 92 and 96), the examiner is requested to point out with particularity (by column and line) where in Dower there is any motivation to select that particular sequence out of the literally millions of sequences described in Dower. Specifically, Dower gives a generic formula for the peptides disclosed therein as having a core sequence defined by the formula $X_1X_2X_3X_4X_5X_6X_7$ and then defines the possible amino acid choices for each of the variables. The following table summarizes the possibilities disclosed by Dower:

Variable	X_1	X_2	X_3	X_4	X_5	X_6	X_7
Number of Choices	6	9	9	20	12	9	9

Thus Dower's generic formula embraces ***almost nine and a half million different peptides***! (Specifically, 6 x 9 x 9 x 20 x 12 x 9 x 9 = 9,447,840 different peptides.) In fact, given the various ways in which Dower discloses the peptides can be modified, ***Dower actually discloses hundreds of millions of different peptides.*** Specific examples of the ways in which Dower discloses the peptides can be modified include, but are not limited to:

a) replacing peptidyl linkages with:

i) carbamate linkages (9,447,840 additional compounds);

ii) phosphonate linkages (another 9,447,840 compounds);

iii) sulfonamide linkages (another 9,447,840 compounds);

iv) urea linkages (another 9,447,840 additional compounds);

v) -CH2 secondary linkages (yet another 9,447,840 compounds);

vi) alkylated peptide linkages (i.e., still another 9,447,840 compounds).

b) derivatizing the N terminus with:

i) -NRR1 groups (at least 108,000,000 more compounds given the definition of R and R1, assuming "lower alkyl" means C1-C3 alkyl);

ii) -NRC(O)R groups (at least 36,000,000 additional compounds);

iii) -NRS(O)2R groups (another 36,000,000 compounds);

iv) -NHC(O)NHR groups (36,000,000 additional compounds);

v) succinimide groups (still another 9,447,840 compounds);

vi) benzyloxycarbonyl-NH-(CBZ-NH) groups (9,447,840 more compounds);

vii) benzyloxycarbonyl-NH- groups having from 1 to 3 substituents on the ring each of which is selected from four types of groups, two of which are categories of groups (let's say conservatively at least another 216,000,000 additional compounds, although clearly this number should be higher).

These and other modifications disclosed by Dower take the number of compounds disclosed therein to well over 600 million different compounds. It cannot reasonably be argued that one skilled in the art would choose the specific sequence of SEQ ID NO: 1 from these millions of compounds, unless, of course one had the benefit of Applicants' disclosure. Again, in order to

clarify his position, the examiner is requested to point out with particularity (by column and line) where in Dower there is any motivation to select ***that particular sequence*** out of the literally millions of sequences described in Dower.

Absent any suggestion or motivation ***in Dower*** to select a peptide having the specific sequence of SEQ ID NO: 1 from the millions of compounds disclosed by Dower, it is respectfully submitted that the rejection of claims 18-21, 91, 92 and 96 under 35 U.S.C. §103 should be withdrawn.

Turning now to the claims wherein the biologically active peptide inserted into an immunoglobulin molecule or fragment is flanked with a proline at the carboxy terminus (i.e., claims 19, 21, 44, 45, 85, 87-89 and 96), none of the applied references teaches or discloses that the presence of a proline at the carboxy terminus of the inserted biologically active peptide is particularly useful ***compared to any other amino acid at that position***. If it is the Examiner's position that Barbas specifically identifies a particular benefit in having a proline at the carboxy terminus of the inserted "binding site", the Examiner is respectfully requested to identify where in Barbas such teaching or suggestion can be found.

In contrast, it has been surprisingly found by Applicants that a proline flanking the peptide can provide an increase ***in biological activity***. It is these various proline-extended embodiments that are embraced by claims 19, 21, 44, 45, 85, 87-89 and 96. The extensive data presented in the working examples of Applicants' specification support the conclusion that proline extension provides a beneficial and unexpected result compared to other amino acids at the carboxy terminus. The conclusion supported by the data is summarized in the paragraph bridging pages 45 and 46 of Applicants' specification as follows:

> "All clones which demonstrated strong binding, were found to contain a proline just downstream of the 14 amino acid TPO mimetic peptide. Selection by panning of a proline in the downstream linker position represents determination of a surprising amino acid choice which confers improved binding characteristics to the grafted TPO mimetic peptide. Weak binders did not contain this proline although they still contained the TPO mimetic peptide."

Clearly, there is no appreciation in the Barbas PCT application or any of the other applied references that the presence of a proline at the carboxy terminus has any particular effect on a peptide inserted at a CDR of an immunoglobulin.

With respect to the Helms article, the insertion of RIPRGDMP into an immunoglobulin CDR1 or CDR3 is disclosed. Initially it is noted that these substitutions were made to study conformational effects, and not to assess the biological activity of the inserted peptide. Also, it appears that the "peptide" being inserted in RIPRGD, in which case the carboxy terminus would be flanked by M, not P. Significantly, Helms does not report the degree of biological activity of the inserted peptide, but only the effect on folding of the immunoglobulin. Thus, Helms provides no guidance as to the benefits discovered by Applicants of flanking with a proline at the carboxy terminus of an inserted peptide ***on the activity of the peptide***.

For all of the foregoing reasons and for the reasons stated in Applicants' previous response, the Barbas PCT application does not, alone or in combination with Dower, render obvious any of claims 19, 21, 44, 45, 85, 87-89 and 96. Accordingly, the rejection of claims 19, 21, 44, 45, 85, 87-89 and 96 under 35 U.S.C. §103 is deemed appropriate and is respectfully requested.

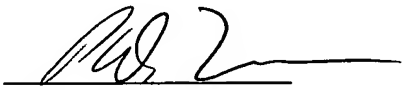
With respect to claims 86 and new claim 97-99, the Office Action contends that on page 32 the Barbas PCT discloses 6 to 50 nucleotides, thereby disclose in 2 flanking amino acids. Applicants disagree with this reading of the Bartbas PCT application. The reference to 6 to 50

nucleotides on page 32 relates to the "Y" variable in the formula -X-[MNN]$_a$-Y-[MNN]$_b$-X- which appears on page 31 of the Barbas PCT. Thus, the reference to 6 to 50 nucleotides on page 32 does not teach or suggest 2 flanking amino acids as that phrase is used in claims 86 and 97-99. Accordingly claims 86 and 97-99 are believed to be immediately allowable.

With respect to claim 96, it is admitted in the Office Action that neither the Barbas PCT application nor Dower teach a peptide comprising the sequence of SEQ ID NO: 2. None of the other applied references are alleged to contain relevant teaching with respect to SEQ ID NO: 2. Accordingly claim 96 is believed to be immediately allowable.

In view of the foregoing amendments and remarks, this case is believed to be in condition for allowance. Such early and favorable action is earnestly solicited.

Respectfully submitted,



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